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(54) Intravascular prothesis

(57) An intraluminal prothesis able to expand radially regarding to a central axis, inside of a body lumen, for example an artery, is presented. The prothesis consists of a series of filaments describing a cylindrical prothesis contour. Each filament consists of a series of curves, each curve having at least a lowest point and a top. Between the adjacent filaments there are gaps. Each gap is bridged by an axial omega shaped element as a connecting part. Each connecting part is attached to adjacent filaments the height of the tops so that the prothesis shortening occurs at radial expansion. Other elements can be placed between the adjacent peripheral elements to obtain a different grade of flexibility between the adjacent filaments. The specific configuration of the prothesis allows further treatment of the branches by the prothesis.

By using water guided laser cutting technology and specific electrochemical polishing technology a more biocompatible prothesis is obtained, causing less thrombogenicity and less foreign body reaction.

By covering an intraluminal prothesis with a titaniumnitride coating the biocompatibility of the prothesis is improved.

By applying perforations or holes, an intraluminal prothesis can be used to locally administer medicines, genes and or other substances to prevent in this way thrombotic occlusions and/or neointimal hyperplasia and prothesis narrowing. Using this specific perforated prothesis design the total drug capacity can be increased and also the drug release time prolongs significantly.

EP 1 132 058 A1

Description

[0001] The following invention concerns intraluminal protheses with a general cylindrical configuration. The protheses can be implanted in a body lumen, for example an artery, and be expanded radially. More in detail we propose here radially expandable intravascular protheses that show little or none axial shortening when they expand radially, that are sufficiently flexible for treating tortuous body lumina and that are configured in such a way that they allow further treatment of side branches.

[0002] By using water-guided laser technology and specific electrochemical polishing techniques this prothesis becomes a superior biocompatibility, which results in a reduced probability of thrombogenicity, neointimal hyperplasia and intraluminal narrowing of the prothesis after intraluminal implantation.

[0003] Further improvement of the biocompatibility of this prothesis is obtained by applying a titanium nitride coating.

[0004] To reduce the foreign body reaction against the prothesis, a special configuration was designed to cover the prothesis optimally by means of a coating impregnated with medicine.

[0005] For this purpose small holes and even perforations were made in the prothesis, admitting to load the prothesis with a dose of medicine up to a thousand times higher compared to a none perforated prothesis. In this way a very biocompatible intraluminal prothesis is obtained which can also be used as a vehiculum for releasing and or deposit medicines locally.

CONFIGURATION DESCRIPTION

[0006] For a while we are confident with intraluminal protheses. These can be implanted in a lumen, for example an artery, to strengthen, support or repair the lumen. With coronary balloon dilatation for example, often a prothesis is implanted in the place where a coronary artery is injured or where it tends to collapse. Once implanted, the prothesis strengthens that part of the artery in a way the blood flow is ensured. A prothesis configuration which is extremely suited for implantation in a body lumen, is a cylindrical prothesis which can radially expand from a first small diameter to a second larger one. Such protheses can be implanted in the artery by placing them on a catheter and transporting them through the artery to the desired location. The catheter is provided with a balloon or another expansion mechanism which exerts a radial outwards pressure on the prothesis so that the prothesis expands to a larger diameter. These protheses are sufficiently strong to stay in shape after expansion, even after removal of the catheter.

[0007] Radially expandable protheses are available in a variety of configurations, in this way an optimal efficacy is ensured in different particular situations. The patents of Lau (US Patent nrs. 5,514,154, 5,421,955, en 5,242,399), Baracci (US Patent nr. 5,531,741), Gaterud (US Patent nr. 85,522,882), Gianturco (US Patent nrs. 5,507,771 en 5,314,444), Termin (US Patent nr. 5,496,277), Lane (US Patent nr. 5,494,029), Maeda (US Patent nr. 5,507,767), Marin (US Patent nr. 5,443,477), Khosravi (US Patent nr. 5,441,515), Jessen (US Patent nr. 5,425,739), Hickle (US Patent nr. 5,139,480), Schatz (US Patent nr. 5,195,984), Fordenbacher (US Patent nr. 5,549,662) en Wiktor (US Patent nr. 5,133,732) all contain a sort of radially expandable prothesis for implantation in a body lumen.

[0008] The mentioned intraluminal protheses indeed do have some disadvantages. Many of these expandable protheses are not extremely flexible and have a central axis that remains rather linear when the prothesis is not expanded yet. Due to such a lack of flexibility the insertion of the prothesis in the artery to be correctly placed in the body lumen is hampered. Another problem of the intraluminal protheses is their decrease in axial length at radial expansion. Although the patent of Lau (US Patent nrs. 5,514,154) attempts to reduce the axial shortening, it fails to succeed entirely.

[0009] When a prothesis is placed in the artery or in another lumen, the implantation has to be performed precisely in the desired place. Intraluminal protheses are often exactly placed before their expansion, but due to the expansion the axial shortening causes that the prothesis finally does not turn up in the correct place.

[0010] In addition the determination of the exact location of a prothesis during an implantation in a lumen is difficult, although a highly qualitative medical monitoring system is available. The problem of the exact place determination of the prothesis enlarges the problem of the precise and exact placement. There exists a need for a radially expandable prothesis presenting little or none axial shortening at radial expansion and that can be located without difficulty using medical imaging systems during the implantation. Another frequently occuring problem is the occlusion of the side branches. In the case of coronary arteries this can cause a myocardial infarction .

[0011] Another very considerable problem is the insufficient hemocompatibility of intraluminal protheses, when they are implanted intravascularly. They can cause acute or subacute thrombotic occlusions due to thrombus formation resulting in a considerable morbidity and even mortality. Furthermore these protheses evoke a foreign body reaction with a considerable inflammation all around the prothesis inducing fibromuscular cellular proliferation and narrowing of the prothesis.

1) DESCRIPTION OF THE BASIC DESIGN OF THE ENDOVASCULAR PROTHESIS

[0012] This invention is about a radial expandable prothesis that presents little or none axial shortening at radial expansion. The prothesis consists of filaments describing the outline of the cylindrical contour. Each prothesis filament connects to a separate surface at right angles to a central axis of the cylindrical contour of the prothesis and parallelly with other surfaces of the adjacent filaments. The prothesis can exist of a variable amount of filaments which all constitute the prothesis. At least two filaments are necessary, including a first and a second ending filament to determine the extremities of the prothesis contour.

[0013] These filaments all show a waving contour in the shape of consecutive omegas. Consequently each filament is composed of a number of turns with lowest points and tops zigzag crossing over the length of each filament. The lowest point is the most distant from the adjacent filament and the top is the most closely situated to the adjacent filament. Figure 1 shows a typical configuration with 12 turns, a number that can vary from 3 to 36 turns. The size of each filament, provided as the distance between lowest point and top, changes when the prothesis expands radially, mostly the size diminishes. In Figure 1 a typical configuration is shown with a distance of 1,5 mm between the lowest point and top, this distance however can vary from 0,5 ot 5 mm.

[0014] The end filaments filaments are attached to adjacent intermediate filaments by means of connecting parts in the shape of an omega that act as axial elements joining two adjacent filaments. Such connecting parts are also able to fasten together intermediate filaments. Each connecting part is attached to the adjacent filaments with a first connection point to the one end of the connecting piece and a second one to the other end. Both connecting points are situated in the tops of the filaments. Thus the connecting points are bridging the distance/opening between adjacent filaments with the interstice as maximal width. Not neccesarily all perforations are bridged with axial connecting parts. Separate outlined intermediate elements can be joined together by means of junctions that are connected with the intermediate elements on locations distant of the lowest points. Depending on the flexibility needs of the prothesis a variable number of tops can be provided with connecting parts that link adjacent filaments. In case a higher flexibility is necessary, more tops will stay empty with only a connecting piece between two adjacent filaments. The prothesis is constructed as such that during gradial expansion of the prothesis the filament waves will in a first fase become somewhat larger and than gradually become shorter. To compensate for this shortening the omega shaped interconnections will gradually enlarge resulting in a less axial shortening during gradial expansion.

2) WATER GUIDED LASER TECHNOLOGY TO CUT A METALLIC INTRALUMINAL PROTHESIS

[0015] Laser cutting of metallic tubes for example 316L stainless steel, nitinol and tantalum tubes cause a considerable heat release at the cutting surface, that radiates through the material. The disadvantage is that the metal structure (grain structure) is deformed and that the cutting surface becomes irregular and oxidized. This leads to a considerable foreign body reaction against the implanted prothesis causing narrowing of the prothesis.

[0016] Utilizing water guided laser technology (Laser-microjet® or comparable systems) to cut the omega-prothesis we were able to diminish these disadvantages.

1) The water jet continuously removes the burnt metal particles, resulting in a better cutting surface.
2) Thanks to the continuous water-cooling, the heat penetration is lower, causing quasi no deformation of the metal grain structure.

[0017] As an example we provide here the specific conditions to apply the water guided laser cutting system. Stainless steel tubes with a diameter of 0.0625 inch (1.585 mm) with a wall thickness of 0.004 inch (0.1 mm) were placed on a continuous rotating holder and cutted with a Haas laser at a frequency of 100 Hz, pulse duration of 0.15 ms, voltage 510 Volt, head diameter of 60 µm and water pressure of 150 bar. Comparing the samples with conventional laser cutted stents, the surface looked much brighter and less blackened. SEM examination showed a much more regular surface. Implantation of these stents after degreasing, ultrasonic cleaning and sterilisation in porcine coronary arteries resulted in considerably less thrombus formation adjacent to the stent filaments and a moderate inflammatory response at 6 days follow-up. At 6 weeks follow-up area stenosis was 60%. These results however compare favourably with conventional laser cutted stents. Conventional laser cutted stents implanted under the same conditions resulted in a total trombotic occlusion of the stented vessel in 40% of the cases, an abundant inflammatory response at 6 days follow-up and an area stenosis of 86% at 6 weeks follow-up. This water guided laser technology can be used to cut any other coronary stent or endovascular prothesis out of a metallic tube.

3) ELECTROCHEMICAL POLISHING OF A METALLIC INTRALUMINAL PROTHESIS

[0018] Surface characteristics of metal intraluminal prothesis are determing the human foreign body response to the

intraluminal prothesis. Therefore optimal surface characteristics are critical for the acute and late patency of an intraluminal prothesis. To further optimize the cutting surface, specific electrochemical polishing techniques were used to optimize the surface characteristics of intraluminal protheses. Depending on the material used, specific chemical solutions were developed for optimal electrochemical polishing of protheses.

BASIC PRINCIPLES OF ELECTROPOLISHING

[0019] Electropolishing is a process by which metal is removed from a work piece by passage of electric current when the work piece is immersed in a liquid media (electrolyte). The work piece is connected to the anodic terminal, while the cathodic terminal is connected to a suitable conductor. Both anodic and cathodic terminals are submerged in the solution, forming a complete electrical circuit. The current applied is direct (DC) current. In this process, the work piece is dissolved, adding metal ions to the solution. When a current passes through the electrolyte, a liquid layer of anodic dissolution products is formed on the surface of the anode; this layer has a higher viscosity and greater electrical resistivity than the bulk of the electrolyte. The thickness of the liquid layer on a rough surface differs from site to site. The current density is non-uniform as result of such non-uniform liquid layer; i.e. it is higher on peaks than in crevices. Thus, peaks dissolve more rapidly than crevices, this, therefore, produces a surface-levelling effect.

[0020] Furthermore electrochemical polishing results in a superficial oxide layer (passivation) which plays also an important role in the biocompatibilisation of a foreign body.

[0021] The quantity of metal removed from the work piece is mainly proportional to the amount of current applied and the time during which the current is applied. In addition, the geometry of the work piece can affect the distribution of the current and, consequently, has an important bearing upon the amount of the metal removed in local area.

FACTORS AFFECTING THE ELECTROPOLISHING PROCESS

[0022] The mode of anodic dissolution of a metal may depend on its nature, the surface state, the composition of the electrolyte, and the temperature, current density and stirring during the electropolishing process.

[0023] Electrolytes used in electropolishing should satisfy the following requirements:

1) high-quality polishing at low voltages and current densities,
2) wide working range of anodic current densities and temperature,
3) a high stability (during operation and upon storage) and long service life,
4) absence of attack on the metal when curent does not flow,
5) electrolyte should consist of cheap, readily available materials and should not present any safety hazards,
6) recovery after a certain period of service should be simple, e.g. by additions of necessary components,
7) the throwing power of the bath should be good, i.e. samples of complex shape should dissolve uniformly over their entire surface,
8) the ohmic resistivity should be low, i.e. the required current density should be obtained at a low voltage,
9) the electrolyte should be suitable for use in the electropolishing of many metals.

[0024] The anodic potential, the anodic current density, and the applied voltage are the main electrical parameters of the electropolishing process. The process is controlled on the basis of the anodic current density and sometimes on the basis of the applied voltage. For any metal and electrolyte system, there should be a certain optimal anodic current density, which provides the highest-quality electropolishing.

[0025] The temperature of the electrolyte has a marked effect on the polishing quality. A range of optimum temperatures should exist for any metal-electrolyte system. A drop in the temperature increases the viscosity of the electrolyte and thus reduces the rate of diffusion of anodic dissolution products from the anode surface to the bulk of the electrolyte.

[0026] The electropolishing time should decrease with increasing current density or with decreasing initial roughness of the surface. The initial roughness and the state of the surface also affect electropolishing quality. Before electropolishing, the surfaces must be degreased and cleaned in organic solvents or by chemical etching in suitable solutions. Stirring is used in cases that the anode is coated with some soluble films or it is necessay to remove bubbles adhering to the surface. Stirring of the electrolyte requires an increase in the current density. The cathodes used in electropolishing should not be attacked in the polishing solution. The surface area of the cathode must be much grater than the surface area of the polished work piece. This ensues a more uniform current distribution, reduces cathodic polarisation and reduces power losses. After the electropolishing, the work pieces should be washed with water or other solvents in order to remove residues of the electrolyte or the anodic dissolution products.

DESCRIPTION OF ELECTROCHEMICAL POLISHING TECHNIQUES FOR NITINOL AND TANTALUM ENDOLUMINAL PROTHESIS

[0027] The electropolishing device that we used was self-designed. A glass container (150 ml) was used as container for the electrolyte. A DC rectifier (Polipower, Struers, Denmark) was employed as a power supply. A nitinol sheet material (length 15 cm, width 2.5 cm and thickness 0.2 cm) was selected as cathode. As shown in Figure 2, the as-received samples were first cleaned with an alkaline solvent with a detergent additive in an ultrasonic bath for more than ten minutes. They were then cleaned in distilled water with an ultrasonic agitation device for more than ten minutes. Since the sheet materials were covered by a black oxide film, they were pickled at room temperature in an acid solution as follows: 2 ml hydrofluoric acid (38-40%) and 40 ml nitric acid (14M) for different time durations in a glass container (50 ml). By observation of the change of the surface state of these sheet samples, a time of seven minutes was finally chosen because the black film just disappeared at this time duration. After pickling, the samples were rinsed in distilled water with an ultrasonic agitation device for more than 10 minutes. After the preparation processes above, electropolishing was then studied with several selected electrolyte mixtures shown in Table 1. Solutions (i) and (ii) were used for electropolishing. Chemical polishing was also evaluated using the solutions (iii) and (iv) in order to have a comparison of the chemical polishing effect with electrochemical polishing.

Table 1.

Selected mixtures for polishing nitinol alloy sheet materials		
Solution		**Concentration**
(i)	perchloric acid (70%) acetic acid (99,8%)	6 ml 94 ml
(ii)	perchloric acid (70%) acetic acid (99,8%)	5 ml 100 ml
(iii)	H_2O_2 HF	50 ml 5 ml
(iv)	H_2O_2 HF	75 ml 5 ml

[0028] Several conditions were selected for the different polishing mixtures in order to compare the differences in the effect of polishing and then to optimize the condition and effect of polishing, which is shown in Table 2. Firstly, as shown in Table 2 (a), the electrolyte (i) was used with a fixed applied voltage for different times to test the electropolishing conditions. The effects were evaluated visually and with optical microscopy. Secondly, the conditions of fixed time and applied voltage were studied as well as that of some other selected times (Table 2 (b)). Then, the electrolyte (ii) was used and the conditions were changed similar to those of electrolyte (i) (Table 2 (c) and Table 2 (d)). The samples were also immersed in different mixtures of acids for different times, as shown in Table 2 (e).

Table 2. The processing conditions for polishing nitinol alloy sheet material

[0029]

Table 2 (a):

Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)
Electrolyte (i)	30	0.2 ~ 0.3	2
			3
			4 ~ 5
			6
			8

Table 2 (b):

Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)
Electrolyte (i)	5	0.023	10
	10	0.045	10
	15	0.1	10 and 15
	20	0.16	3,15 and 10
	25	0.22	3,5 and 10

Table 2 (c):

Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)
Electrolyte (ii)	30	0.15 ~ 0.25	2
			3
			4 ~ 5
			6
			8
			10

Table 2 (d):

Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)
Electrolyte (ii)	20	0.15	3
			6
	25	0.17	3
			6

Table 2 (e):

Electrolyte	Time (min.)
Electrolyte (iii)	3,9 and 15
Electrolyte (iv)	3,9 and 15

[0030] Most of the polishing processes were conducted at room temperature without stirring. A part of the polishing processes however was done at an elevated temperature. Also the effect of stirring on the polishing process was explored. The reason that the applied voltage was selected as one of the controlling parameters was that the current was not stationary during the process of electropolishing and the stents had a special shape of mesh so that the current density was very difficult to calculate accurately. All of the polished samples were rinsed in distillated water with an ultrasonic agitation device for more than 10 minutes and then stored in ethanol. Evaluation of the effects of the polishing was performed by means of optical microscopy and scanning electron microscopy.

ELECTROPOLISHING OF A NITINOL ENDOVASCULAR PROTHESIS, FOR EXAMPLE A CORONARY STENT

[0031] The same electropolishing cell as that for the sheet material was employed. First of all, due to the finite stent samples and their high cost, electropolishing of some nitinol alloy wires of different diameters of 1 mm, 0,3 mm and 0,5 mm were performed with different parameters in order to find an optimal way of electropolishing the nitinol alloy stents. All the wires were covered with a black oxide layer. They were ground with rough abrasive paper to remove the oxide layer. The different conditions for the electropolishing are shown in Table 3.

Table 3.

The selected processing conditions for electropolishing nitinol alloy wires			
Electrolyte	**Applied voltage (V)**	**Anodic current (amp)**	**Time (min.)**
Electrolyte (ii)	30	0.21	2, 3, 4 ~5, 8
	25	0.2	2, 3, 4 ~5, 8
	20	0.18	2, 3, 4 ~5, 8

[0032] The selection of these conditions was based on our observations of the electropolishing of sheet materials. The removal was measured with a micrometer (Mitutoyo Digimatic micrometer).

[0033] The as-received stents were first cleaned with an alkaline solvent with detergent additive in an ultrasonic bath for more than ten minutes in order to remove the contaminants of the surface. All the samples were then cleaned in distilled water with an ultrasonic agitation device for more than ten minutes. Considering the oxide layer formed during the process of fabrication, the stents were pickled for 2, 4 and 6 minutes at room temperature in the following acid solution: 2 ml hydrofluoric acid (38-40%) and 40 ml nitric acid (14M).

[0034] By observation with optical microscopy, a time of nearly six minutes was chosen as the optimum pickling time of the stents. The samples were then rinsed in distilled water with ultrasonic agitation for more than 10 minutes. After pickling and rinsing, electropolishing was done without stirring at room temperature using the conditions shown in Table 4.

Table 4.

The selected processing conditions for electropolishing nitinol alloy stents			
Electrolyte	**Applied voltage (V)**	**Anodic current (amp)**	**Time (min.)**
Electrolyte (ii)	30	0.25	3
	25	0.17	1, 1, 3, 5
	20	0.15	1,1,5~2

[0035] These conditions were selected according to the results of the electropolishing of sheet materials and wires, considering the specific thin shape of mesh of the stents. After electropolishing, the samples were rinsed in distilled water with an ultrasonic agitation device for more than 10 minutes. Electropolishing of the stents without the pre-treatment of pickling was also done in order to check whether or not the oxide layer can be removed as well as to investigate the effects of pickling on the electrochemical polishing of the stents for the following condition (Table 5).

Table 5.

The conditions for electropolishing the stents without pickling			
Electrolyte	**Applied voltage (V)**	**Anodic current (amp)**	**Time (min.)**
Electrolyte (ii)	20	0.15	1.5 ~ 2

[0036] Table 6 summarizes all the results of applied polishing processes for nitinol alloy materials.

Table 6. The comparison of the different polishing processes

[0037]

Table 6 (a):

Process	Material	Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)	Result
Electropolishing	Sheet	Electrolyte (i)*	30	0.2 ~ 0.3	2	less-polished
					3	general
					4 - 5	good
					6	overpolished
					8	overpolished
			5	~ 0.023	10	no changes
			10	~ 0.045		no changes
			15	~ 0.1		small changes
			20	~ 0.16		general
			25	~ 0.22		general
			15	~ 0.1	15	attacked
			20	~ 0.16	3	general
			25	~ 0.22		general
			20	~ 0.16	5	good
			25	~ 0.22		good

* perchloric acid (70%) 5 ml, acetic acid (99,8%) 100 ml

Table 6 (b):

Process	Material	Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)	Result
Electropolishing	Sheet	Electrolyte (ii) **	30	~ 0.2	2	general
					3	good
					4 ~ 5	better
					6	general
					8	overpolished
			20	~ 0.15	3	general
			25	~ 0.17		general
			20	~ 0.15	6	good
			25	~ 0.17		good
Chemical polishing	Sheet	Electrolyte (iii) #	-	-	3	no changes
			-	-	9	rough
			-	-	15	rough
		Electrolyte (iv) ##	-	-	3	no changes
			-	-	9	rough
			-	-	15	rough

Table 6 (b): (continued)

Process	Material	Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)	Result
# H_2O_2 50 ml, HF 5 ml ## H_2O_2 75 ml, HF 5 ml						

Table 6 (c):

Process	Material	Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)	Result
Electropolishing	Wire	Electrolyte (ii)	30	~ 0.21	2	general
					3	good
					4 ~ 5	overpolished
					8	overpolished
			25	~ 0.2	2	general
					3	good
					4 ~ 5	overpolished
					8	overpolished
			20	~ 0.18	2	general
					3	good
					4 ~ 5	overpolished
					8	overpolished

Table 6 (d):

Process	Material	Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)	Result
			30	- 0.25	3	overpolished
			25	~ 0.17	1	general
Electropolishing	Stent	Electrolyte (ii)			1.5	general
					3	overpolished
			20	~ 0.15	1	good
					1.5 ~ 2	better

[0038] All these studies were conducted at room temperature without agitation. Several elevated temperatures (25°C and 30°C) were used, but no large changes on the results of polishing were found. As to the agitation, it gave relatively bad results for polishing sheet materials. During observation of the polishing process, dark spots appeared on the surface, and by means of optical microscopy, these surfaces were proven to be rough. In addition, bubbles were found adhering to the surface of the sample when polishing.

[0039] Two electrolytes were selected:

(i) perchloric acid (70%) 6 ml, acetic acid (99,8%) 94 ml
(ii) perchloric acid (70%) 5 ml, acetic acid (99,8%) 100 ml

[0040] Finally electrolyte (ii) was selected for electrochemical polishing of either sheet materials or stents (Table 1). During experiments with electrolyte (i), no change on the surface of the sheet material was found using voltages of 5 V and 10 V, even for more than ten minutes. This is consistent with the fact that electrochemical polishing takes place only when the current density is higher than that noted at the critical point. Current density and voltage are closely

related in polishing. As voltage increases there is an increase in current density generally. The surface is attacked with a voltage of 15 V for 15 minutes. This might be the effect of electroetching. Electroetching is a comparatively slow process and its current densities are often smaller than those with electropolishing. Thus, it is suggested to select the voltages of 20 V, 25 V and 30 V for this nitinol alloy material from the results in Table 6.

[0041] The duration of polishing for sheet materials is longer than that of wires and much longer compared to that of stents. This might be because of the difference in degree of surface roughness of these materials and related to the thin size of the stent filaments. A time, up to six or eight minutes is so long that it causes overpolishing for the sheet materials. However, polishing time of three minutes has caused overpolishing for the stents. Figure 4 shows two over-polished surfaces of stents. One is apparently attacked, which shows a very bad quality and the size of the stent did not remain uniform. Another one has a relatively smooth and uniform surface but the amount removed might be so large that the stent has been apparently too thin to have enough strength to be used. Thus, the amount removed from stents should be controlled very carefully so that the mechanical strength of the stent is maintained while the smoothness is obtained by means of electrochemical polishing.

[0042] The smooth surface can not be obtained by means of chemical polishing alone in this experiment. Chemical polishing is not sufficient to polish these nitinol alloy materials. The optimal conditions for electrochemical polishing of nitinol stents are shown in Table 7. These optimal conditions will be somewhat different for each particular nitinol sample and will have to be restudied for each particular nitinol prothesis depending on the design and mesh tickness used.

Table 7.

The optimal condition for electropolishing of nitinol alloy stents			
Electrolyte	**Applied voltage (V)**	**Anodic current (amp)**	**Time (min.)**
Electrolyte (ii)**	20	0.15	1.5 ~ 2

** perchloric acid (70%) 5 ml, acetic acid (99,8%) 100 ml

INFLUENCE OF THE PREPARATION WITH ACIDIC PICKLING ON ELECTROCHEMICAL POLISHING

[0043] The conditions and results of electrochemical polishing stents with no preparation are summarized in Table 8.

Table 8.

The result of electropolishing stents with no pickling						
Process	Material	Electrolyte	Applied voltage (V)	Anodic current (amp)	Time (min.)	Result
Electropolishing	stent	Electrolyte (ii)	20	~ 0.15	1.5 ~ 2	Bad

[0044] Figure 5 shows the morphology of the stent surface electropolished without acidic pickling. It is very clear that the rough oxide layers still adhere to the bottom surface of the stent and reveal an even worse quality than the as-received one. Thus, it can be concluded that the heavy oxide layer can not be removed by means of electrochemical polishing alone, i.e. the preparation of pickling is necessary for electrochemical polishing of nitinol alloy stents which are covered with heavy oxide layers.

[0045] In this experiment, acidic pickling was explored for stents at room temperature with acidic solution: 2 ml hydrofluroic acid (38-40%) and 40 ml nitric acid (14M).

[0046] Several periods of time were selected. The description of the effects of this pickling process is summarized in Table 9.

Table 9.

The effects of acidic pickling for preparation of electropolishing stents					
Time (min.)	1	2	4	6	8
Result	no change	no change	general	good	overpickled

[0047] During the immersion times 1 min. and 2 min., there was no apparent change on the surfaces compared with that of the as-received samples when studied by optical microscopy. For 4 min., 6 min. and 8 min. the oxide layers were removed. There were still some oxides adhered to the surface immersed for 4 min., whereas the oxide layer was removed completely for incubation times of 6 min. and 8 min. Thus, a time of 5 to 7 min. was selected as optimal

pickling time for nitinol stents.

POLISHING OF A TANTALUM INTRALUMINAL PROTHESIS, FOR EXAMPLE A CORONARY STENT

[0048] This study was done by means of electrochemical polishing and chemical polishing in order to find an optimal condition of polishing of tantalum stents and to obtain a better quality of the surface of tantalum stents. The as-received materials were non-polished tantalum stents. The polishing cell was designed similar to that for nitinol alloy material mentioned before. A glass container (100 ml) was used as an electrolyte container. A DC rectifier (Polipower Struers) was employed as a power supply. For cathode, a graphite stick was chosen with a diameter of 10 mm. Several electrolytes were selected for this study, as shown in Table 10.

Table 10.

The selected electrolytes for polishing tantalum stents		
Solution		**Concentration**
(I)	acetic acid	20 ml
	H_2SO_4	50 ml
	HF	10 ml
(II)	H_2SO_4	90 ml
	HF	10 ml
(III)	H_2SO_4	50 ml
	HNO_3	20 ml
	HF	20 ml

[0049] The electrolyte (I) and (II) were used for electrochemcial polishing, and the electrolyte (III) was used for chemical polishing. The as-received samples were first cleaned with an alkaline solvent with detergent additive dipped in an ultrasonic bath for more than ten minutes. All the samples were then cleaned in distilled water with an ultrasonic agitation device for more than ten minutes. After degreasing, the samples were treated by means of acidic pickling for several amounts of time: 2.5, 5, 7.5, 10 and 20 minutes in the following solutions: HF 48-51% 5.6 ml, H2SO4 95-97% 1 ml, HNO3 65% 8 ml, H2O 8 ml. The samples were then cleaned in distilled water with an ultrasonic agitation device for more than ten minutes. According to the effects observed by means of optical microscopy, ten min. was chosen as the best pickling time. After pickling, the samples were polished with the selected electrolytes. The conditions are given in Table 11.

Table 11.

The conditions for polishing tantalum stents		
Electrolyte	**Applied voltage (V)**	**Time (min.)**
Electrolyte (I)	2.5, 5, 7.5, 10	2
	5	0.5, 1, 2, 3
Electrolyte (II)	15	3, 6, 9, 12
	10, 15, 20	9
Electrolyte (III)		2, 4, 6

[0050] The voltage was selected as the controlling parameter because the current density was difficult to determine with the specific shape of the stents. The electropolishing of the as-received samples without degreasing and pickling was also done in order to check whether or not an oxide layer exists on the surface as well as to investigate the effects of pickling on the electrochemical polishing of the stents. The conditions are shown in Table 12.

Table 12.

. The conditions for electropolishing tantalum stents without degreasing and pickling		
Electrolyte	**Applied voltage (V)**	**Time (min.)**
Electrolyte (I)	5, 7.5	2
Electrolyte (II)	15	6, 9

[0051] After cleaning in distilled water with an ultrasonic agitation device for more than ten minutes, all the polished samples were evaluated with optical microscopy and some of them were then studied by means of scanning electron microscopy. The SEM pictures of both the polished samples and the as-received samples were taken in order to compare their surface qualities.

COMPARISON AMONG THE DIFFERENT POLISHING METHODS

[0052] Table 13 summarizes all the results of the explored polishing processes for the tantalum stents. All these electrochemcial polishing processes were conducted at room temperature with agitation. Prior to the electropolishing processes, both degreasing and pickling were done. Two electrolytes were explored for electropolishing: (I) acetic acid 20 ml, H_2SO_4 50 ml, HF 10 ml, (II) H_2SO_4 90 ml, HF 10 ml.

Table 13.

The comparison of the different polishing processes				
Process	Electrolyte	Applied voltage (V)	Time (min.)	Result
Electropolishing	Electrolyte (I)	2.5	2	general
		5		better
		7.5		good
		10		overpolished
		5	0.5	less polished
			1	general
			2	good
			3	overpolished
	Electrolyte (II)		3	less polished
		15	6	general
			9	good
			12	overpolished
		10	9	less polished
		15		good
		20		general
Che-polishing	Electrolyte (III)		2	rough
			4	rough
			6	rough

[0053] From the evaluation of the effects of polishing by means of optical microscopy, electrolyte (I) gave a relatively better effect; therefore it was concluded to be the preferred electrolyte.

[0054] The voltages 2.5 V, 5 V, 7.5 V and 10 V were explored respectively with electrolyte (I) for 2 min. The voltages of 2.5 and 10 V provided relatively bad results. 5 V revealed the best results among these voltages. Fixing the voltage to 5 V, the times 0.5 min., 1 min. and 3 min. were selected in order to compare the results. The result was that the voltage 5 V and the time 2 min. in conjunction with electrolyte (I) were optimal parameters for electrochemical polishing

this kind of tantalum stents. Electrolyte (II) was also used with some changed parameters. Several times were explored with fixed voltage 15 V. It was found that 9 min. causes the best result among these times, and either 3 min. or 12 min. resulted in a bad surface quality. Then the time 9 min. was fixed and voltages were changed to explore their effects on the polishing. 15 V gave a relatively better result than 10 V and 20 V. Similar to the results in the experiment of polishing nitinol alloy materials, chemical polishing could not lead to a sufficient smooth surface. The conditions and the results were summarized in Table 13.

INFLUENCE OF SAMPLE PREPARATION WITH DEGREASING AND PICKLING ON ELECTROCHEMICAL POLISHING

[0055] The conditions and the results of electrochemical polishing with no pickling were summarized in Table 8. SEM evaluation of the stent surface electrochemically polished without degreasing and acidic pickling showed disappointing results. It was clear that the rough oxide layers still adhered to the side surface of the stent. The surface of the polished sample reveals a worse quality than that of the as-received one. Thus, it can be concluded that the heavy oxide layer can not be removed only by means of electrochemical polishing, i.e. the preparation of pickling is necessary before electrochemical polishing the tantalum stents which are covered with heavy rough oxide layers. Degreasing was accomplished by an alkaline solvent with detergent additive. Pickling was used to remove the heavy oxide layer and normally done with alkaline or acidic solutions. In this experiment, acidic pickling was explored at room temperature with acidic solutions: HF 48-51% 5.6 ml, H2SO4 95-97% 1 ml, HNO3 65% 8 ml, H2O 8 ml.

[0056] Several time periods were selected. The description of the effects of this pickling process was summarized in Table 9. For the immersion times 2.5 min. and 5 min., there were no apparent changes on the surface compared to that of the as-received samples by observation with optical microscopy, whereas for a time more than 7.5 min. some precipitates began to appear in the solutions during the experiment. The immersion time 20 min. caused attack on the surface. Thus, the pickling time should be controlled seriously in order to remove all the oxide layers and to avoid surface attack. In this study 6 min. was found to have a relatively good effect.

ELECTROCHEMICAL POLISHING: CONCLUSIONS NITINOL

[0057] For nitinol a pre-treatment using a solution of 2 ml of hydrofluoric acid and 40 ml of nitric acid (14 M) for 5 to 7 minutes is suggested. For electrochemical polishing optimal results were found with 5 ml of perchloric acid (70%) and 100 ml of acetic acid (99,8%) using an anodic current of 0,15 amp and a voltage of 20 V during 1 to 3 minutes (Table 7).

TANTALUM

[0058] For tantalum a solution of 20 ml of acetic acid, 50 ml of hydrosulphate and 10 ml of hydrofluoride or a solution of 90 ml of hydrosulphate and 10 ml of hydrofluoride was used. The voltage was 5 V during a period of 1 to 5 minutes and the pre-treatment was done using a solution of 5,6 ml of hydrofluoride (48-51%), 1 ml of hydrosulphate (95-97%), 8 ml of hydronitrate and 8 ml of water during 5 to 7 minutes (Table 14).

Table 14.

The optimal conditions for electropolishing the tantalum stents		
Electrolyte	**Applied voltage (V)**	**Time (min.)**
Electrolyte (I)***	5	~ 2

*** acetic acid 20 ml, H_2SO_4 50 ml, HF 10 ml

[0059] This treatment resulted in a further reduction of thrombogenicity, of foreign body reaction and of prothesis narrowing. These inventions can be used for any stent or endovascular prothesis made of nitinol or tantalum.

4) TURNING A METALLIC ENDOVASCULAR PROTHESIS MORE BIOCOMPATIBLE USING A TITANIUMNITRIDE COATING

[0060] A metal prothesis always causes a kind of foreign body reaction after intraluminal implantation.

[0061] To improve the biocompatibility of the prothesis, fine coatings can be applied. Experiments with titanium nitride coatings (1-15 µm) showed a significant decreased foreign body reaction in a porcine coronary model, what did result in a significant amelioration of the minimal luminal diameter of the prothesis at follow-up.

DESCRIPTION OF THE TITANIUM NITRIDE COATING. EVALUATION OF THE TiN COATED ENDOVASCULAR PROTHESIS IN A PORCINE CORONARY MODEL

[0062] Titanium nitride (TiN) coatings have proved their efficiency in increasing the lifetime of cutting tools. Their tribological properties are widely known and their use in bioengineering applications as a biomaterial has been considered, particularly as a wear-resistant coating for Ti6A14V orthopaedic implants. The tests undertaken showed that wear was reduced, that the TiN friction coefficient was low and that TiN presented good chemical stability.

[0063] We used TiN (5 μm) to coat an intraluminal prothesis and demonstrated improved biocompatibility.

[0064] To illustrate the invention a coronary stent of a coil-type design, as described in US patent 5,183,085 was used. It consisted of a preconditioned, non ferromagnetic, highly polished stainless steel wire (AISI 316L) with a diameter of 0.18 mm. This design allows folding (radial compression) on any conventional balloon, resulting in a low profile 6F guiding catheter compatible stent delivery system. Percentage of axial shortening upon expanding the balloon is less than 5% and the stent is available in lenghts from 12 mm up to 40 mm allowing customized stenting. These stents are available as bare stents or as mounted stents. In the present example stents of a length of 16 mm were used. For this invention any laser cut stainless steel mesh stents or any intraluminal metal prothesis can be used as well.

POROUS TiN COATING

[0065] The vacuum deposition techniques of physical vapor deposition (PVD) and chemical vapor deposition (CVD) are well known for their ability to form TiN coatings of different structures and stoichiometries. Porous TiN can be generated in a reactive sputtering process, which is a special PVD method.

[0066] In the reactive sputtering process, Ar ions are produced by a glow discharge and accelerated against a Ti target. The ions impinging on the Ti lead to the ejection of particles from the target surface. These particles condense on the surfaces in line-of-sight to the target. Additional N2 gas activated in the plasma and the Ti react to yield TiN. The structure of the TiN can be influenced and determined by controlling the deposition parameters like Ar and N2 pressure, target power, substrate bias voltage, and substrate position relative to the Ti target. For certain parameters, the TiN layer grows with columnar structure and shows up to 1000 fold increase in effective surface area. The thickness of the sputtered layer lies around 5 μm. The thickness constancy is ensured by a uniform rotation of the intraluminal prothesis during the sputtering process.

EXPERIMENTAL WORK

[0067] The TiN coated and bare non-coated stents were radially compressed on a balloon catheter (3 to 3.5 mm) and randomly implanted in a series of coronary arteries of 20 domestic cross bred pigs of both sexes, weighing 25 to 30 kg. Ten TiN coated stents and 10 non-coated highly polished stainless steel stents were implanted for comparison. All stent deployments and implantations were successful and resulted in properly stented vessel segments. Six weeks after implantation, control angiography of the stented vessels was performed and subsequently pigs were sacrificed. At that time their average weight was about 70 kg and the vessels had also grown considerably, compared to their size at the time of implantation.

[0068] Angiographic analysis (quantitative coronary angiography) of stented vessel segments was performed before stenting, immediately after stenting, and at follow-up using the Polytron 1000-system as described by De Scheerder et al. in the Journal of Invasive Cardiology 1996;8:215-222. The lumen diameters of the vessels were measured before stent implantation (= pre-stenting artery diameter values), immediately thereafter (= post-stenting values) and at follow-up (= diameters after 6 weeks). The degree of oversizing (%) was expressed as measured maximum balloon size minus minimal stent lumen diameter (measured 15 minutes after stent implantation) and divided by measured maximum balloon size. The late loss value is an indication of hyperplasia and is the difference between the post-stenting value and the diameter at follow-up. The results of the angiographic measurements are summarized in Table 15. Baseline selected arteries, measured balloon diameter and post stenting diameter were similar for the three types. Oversizing and recoil were also similar. At six weeks follow-up a larger minimal luminal stent diameter and a decreased late loss was found for the TiN-coated stents.

Table 15.

Quantitative Coronary Analysis of titanium nitride coated stents		
Mean Artery Diameter (mm)	**Non-coated stent n=10**	**TiN-coated stent n=10**
Pre stenting (mm)	2.52 ± 0.18	2.53 ± 0.27
Balloon size (mm)	2.93 ± 0.16	2.94 ± 0.15

Table 15. (continued)

Quantitative Coronary Analysis of titanium nitride coated stents		
Mean Artery Diameter (mm)	**Non-coated stent n=10**	**TiN-coated stent n=10**
Post stenting (mm)	2.68 ± 0.16	2.71 ± 0.18
Oversizing (%)	16 ± 6	16 ± 7
Recoil(%)	8 ± 4	8 ± 4
6 weeks FU (mm)	2.52 ± 0.29	2.69 ± 0.24
Late loss	0.16 ± 0.28	0.02 ± 0.16

[0069] After the pigs were sacrificed coronary segments were carefully dissected together with 10 mm minimum vessel segment both proximal and distal to the stent. Histopathology, as evaluated by light microscopic examination, was performed on very thin cross-section slices of the stented artery sections. Injury of the arterial wall, due to stent deployment, was evaluated as a first factor and graded according to the method of Schwartz et al. (J.Am. Coll. Cardiol 1992;19:267-274). Likewise, inflammatory reaction at every stent filament site was examined (second factor) by searching for inflammatory cells and graded as well. Appearance of thrombus was evaluated as a third factor and graded. The mean value of every factor for the 10 samples of each of the two stent types was calculated.

[0070] Thrombus formation was decreased in the coated stent group. Also peri-stent inflammation was decreased in the TiN-coated stent group.

[0071] Finally, a morphometric study was carried out on the stented vessel segments at the time of follow-up after six weeks of implantation. The study was made using a computerized morphometry program (Leitz CBA 8000). Measurements of lumen area, lumen inside the internal elastic lamina (= IEL area) and lumen inside the external elastic lamina (= EEL area) were performed on the arterial sites, all in mm2. Neointimal hyperplasia (= IEL area minus lumen area) and area stenosis in % as the ratio of hyperplasia to IEL area were derived therefrom. The results are shown in Table 16.

Table 16.

Morphometry of titanium nitride coated stents		
Mean Cross Section Area (mm2)	**Non-coated stent n=10**	**TiN-coated stent n=10**
Lumen area (mm^2)	1.71 ± 0.66	2.86 ± 0.74
IEL area (mm^2)	3.87 ± 1.39	3.81 ± 1.02
EEL area (mm^2)	5.74 ± 2.06	5.86 ± 2.12
Hyperplasia (mm^2)	2.16 ± 1.48	0.95 ± 0.64
Area stenosis (%)	54 ± 15	25 ± 11

[0072] TiN-coated stents showed an improved lumen area and a decreased neointimal hyperplasia and area stenosis at follow-up. Although the invention has been described for coronary blood vessels, similar results can be obtained for stents and intraluminal prothesis with a TiN-coating in other luminal life stream conducts in animal and human bodies.

5) A LOCAL INTRALUMINAL MEDICINE OR GENE RELEASING SYSTEM

[0073] Several trials with systematically (oral or intravenous) administered anti restenotic medicines after dilatation of narrowed lumina (for example of a coronary arterial atherosclerotic narrowing) failed in consequence of a too limited medicine concentration on the place where the medicine has to act and due to the systemic medicine's side effects when higher doses are administered. For this reason medicines were applied locally, at the place of the organ to be treated. For example in the treatment of coronary stenoses using special catheters, medicines were injected into the vessel wall.

[0074] Disadvantages of this approach are the limited efficiency of the so called local treatment (less than 5% of the administered medicine reaches the target organ) and the increased damage to the target organ due to the local drug administration.

[0075] Another method is the covering of an endoluminal prothesis with a polymer coating and the impregnation of the polymer with a medicine. The disadavantage of this method is the limited capacity of the coating and the too fast

release of the medicine.

[0076] To optimize this system we put holes and even perforations in the endoluminal prothesis. These holes and perforations are filled with the medicine impregnated polymer before implantation. The holes and perforations can vary in size and density. Also microperforations or even micropores can be used to achieve this invention. Furthermore porous metals having micropores can be used to achieve this invention. The condition is that the radial force of the prothesis is not affected. By applying this technique an increment of the local medicine capacity of the prothesis with a factor of one hundred and a considerable prolongation of the duration of medicine release can be obtained (weeks instead of days). Animal experimental research showed a hundredfold tissue concentration of the medicine in a porcine model after implantation of a polymer coated perforated endoluminal prothesis in coronary arteries.

[0077] Furthermore we could prove that the duration of medicine release was significantly longer and that the presence of the medicine in the vascular tissue was significantly longer.

[0078] Polymeric drug eluting surface coatings have been described to improve stent biocompatibility by locally releasing the drug at the target site (European patent application 0623354A1).

[0079] Disadvantages of this system are:

1) the moderate biocompatibility of the polymers used, resulting in an increased inflammatory reaction,
2) because only very thin polymer layers can be used and the contact area is large, the drug release using these coated stents is too fast and because only very thin polymer layers can be applied the total dose of drug loaded on the stent to be locally released is limited

[0080] By making holes or even perforations in the metal structure of the prothesis (Figure 6) and filling these holes and/or perforations with a drug or a polymer coating containing one or more medicines with anti thrombotic and/or anti restenotic properties, a prothesis is developed that very efficiently releases the medicine gradually and puts the medicine directly in contact with the damaged tissue. The prothesis starts to function as a reservoir for the medicine, which is gradually released after implantation of the endoluminal prothesis to carry out its function.

[0081] Instead of conventional medicines also genes can be used that code for certain substances (proteins) having either an anti thrombotic or an anti restenotic action.

[0082] Three significant advantages are obtained by using the perforated prothesis in comparison with the classical polymer covered protheses:

1) The total dose of medicine that can be loaded onto the prothesis increases with a factor of one hundred to one thousand, depending on the size and the amount of perforations.
2) By making only holes instead of perforations, the medicine release can be directed; either towards the tissue surrounding the lumen or towards the lumen itself.
3) The release time of the medicine becomes much longer (weeks instead of days).

[0083] Viewed from one aspect therefore the invention provides a method for making an intraluminal prothesis comprising the steps of:

a) providing a generally cylindrical prothesis body
b) making holes or even perforations in the metal structure of the prothesis
c) applying to the prothesis body a solution which comprises a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent; and
d) evaporating said solvent.

[0084] Viewed from a further aspect the invention provides the use of a solution containing a dissolved polymer and a dispersed therapeutic substance for the manufacture of a therapeutic agent comprising a perforated intraluminal prothesis having a polymeric drug eluting coating.

[0085] Viewed from a still further aspect the invention provides protheses made by the method of the invention. In the method of the invention there is applied to the body of a prothesis and in particular to its tissue-contacting surface, a solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance (i.e. a drug) dispersed in the solvent, and the solvent thereafter is evaporated to leave a drug eluting polymeric substance filling the holes and/or perforations of the prothesis. The inclusion of a polymer in intimate contact with a drug filling up the holes and/or perforations of the prothesis allows the drug to be retained in the prothesis in a resilient matrix during expansion of the prothesis and also slows the administration of drug following implantation. The method of the invention can be used whether the perforated prothesis has a metallic or polymeric surface. The method is also an extremely simple one since it can be effected by simply immersing the perforated prothesis into the solution or by spraying the solution onto the perforated prothesis. The amount of drug to be included in the perforated prothesis can be readily controlled

by changing the size and the amounts of the holes and/or perforations or by using different drug concentrations and or different coating application methods. The rate at which the drug is delivered can be controlled by the selection of an appropriate bioabsorbable or biostabel polymer and by the ratio of drug to polymer in the solution. By this method, drugs such as glucocorticoids (e.g. methylprednisolone, dexamethasone, betamethasone), heparin, hirudin, tocopherol, angiopeptin, aspirin, ACE inhibitors, growth factors, oligonucleotides, and, more generally, antiplatelet agents, anticoagulant-agents, antimitotic agents, antioxidants, antimetabolite agents, and anti-inflammatory agents and also genes can be stored in a perforated prothesis, retained in a perforated prothesis during expansion of the perforated prothesis and elute the drug at a controlled rate. The release rate can be further controlled by using additional barrier coatings or multiple layers of coating with varying drug concentrations. In operation, the perforated prothesis made according to the present invention can deliver drugs to a body lumen by introducing the perforated prothesis transluminally into a selected portion of the body lumen and radially expanding the perforated prothesis into contact with the body lumen. The transluminal delivery can be accomplished by a catheter designed for the delivery of perforated protheses and the radial expansion can be accomplished by balloon expansion of the perforated prothesis, by self-expansion of the perforated prothesis or a combination of self-expansion and balloon expansion.

[0086] Thus the present invention provides a perforated prothesis which may be delivered and expanded in a selected body lumen or conduit without losing a therapeutically significant amount of a drug or gene applied thereto. It also provides a drug or gene containing prothesis which allows for a sustained release of the drug or gene to luminal or conduit tissue.

[0087] The underlying structure of the perforated prothesis used according to the invention can be virtually any perforated prothesis design, for example of the self-expanding type or of the balloon expandable type, and of metal or polymeric material. Thus metal prothesis designs such as those disclosed in US-A-4.733.665 (Palmaz) and US-A-5.603.721 (Lau) could be used in the present invention. The perforated prothesis could be made of virtually any biocompatible material having physical properties suitable for the design. For example, tantalum, nitinol and stainless steel have been proven suitable for many such designs and could be used in the present invention. Also, protheses made of biostable or bioabsorbable polymers such as poly(ethylene terephthalate), polyacetal, poly(lactic acid), poly (ethylene oxide)/poly(butylene terephthalate) copolymer could be used in the present invention. Although the perforated prothesis surface should be clean and free from contaminants that may be introduced during manufacturing, the perforated prothesis surface requires no particular surface treatment in order to retain the coating applied in the present invention.

[0088] In order to provide the coated perforated prothesis according to the present invention, a solution which includes a solvent, a polymer dissolved in the solvent and a therapeutic substance dispersed in the solvent is first prepared. The solvent, polymer and therapeutic substance should of course be mutually compatible. The solvent should be capable of placing the polymer into solution at the concentration desired. Moreover the solvent and polymer should not chemically alter the therapeutic character of the therapeutic substance. However, the therapeutic substance only needs to be dispersed throughout the solvent so that it may be either in a true solution with the solvent or dispersed in fine particles in the solvent. Examples of some suitable combinations of polymer, solvent and therapeutic substance are set forth in Table 17.

Table 17.

Examples of some suitable combinations of polymers, solvents and therapeutic substances		
Polymer	**Solvent**	**Therapeutic substance**
poly(L-lactic acid)	chloroform	dexamethasone
poly(lactic acid-co-glycolic acid)	acetone	dexamethasone
polyether urethane	N-methyl pyrrolidone	tocopherol (vitamin E)
silicone adhesive	xylene	dexamethasone phosphate
poly(hydroxybutyrate-co-hydroxy-valerate)	dichloromethane	aspirin
fibrin	water (buffered saline)	heparin

[0089] The solution is applied to the perforated prothesis and the solvent is allowed to evaporate, thereby filling the perforations and leaving on the perforated prothesis surface a coating of the polymer and the therapeutic substance. Typically, the solution can be applied to the perforated prothesis by either spraying the solution onto the perforated prothesis or immersing the perforated prothesis in the solution. Whether one chooses application by immersion or application by spraying depends principally on the viscosity and surface tension of the solution. In either a coating applied by spraying or by immersion, multiple application steps are generally desirable to provide improved coating

uniformity and improved control over the amount of therapeutic substance to be applied to the perforated prothesis.

[0090] The polymer chosen should be a polymer that is biocompatible and minimizes irritation to the vessel wall when the perforated prothesis is implanted. The polymer may be either a biostable or a bioabsorbable polymer depending on the desired rate of release or the desired degree of polymer stability, but a bioabsorbable polymer may be more desirable since, unlike a biostable polymer, it will not be present long after implantation to cause any adverse, chronic local response. Bioabsorbable polymers that could be used include poly(L-lactic acid), polycaprolactone, poly (lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxyburytate-co-valerate), polydioxanone, polyorthoester, polyanhydride, poly(glycolic acid), poly(D, L-lactic acid), poly(glycolic acid-co-trimethylene carbonate), polyphosphoester, polyphosoester uethane, poly(amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(etheresters) (e.g. PEO/PLA) polyalkylene oxalates, poly(organs)phosphazenes, hydrophylic polymetracrylates and biomolecules such as fibrin, fibrinogen, cellulose, starch, collagen and hyaluronic acid. Also, biostable polymers with a relative low chronic tissue response such as polyurethanes, silicones, and polyesters could be used and other polymers could also be used if they can be dissolved and cured or polymerized on the perforated prothesis such as polyolefins, polyisobutylene and ethylene-alphaolefin copolymers; acrylic polymers and copolymers, vinyl halide polymers and copolymers, such as polyvinyl chloride; polyvinyl ethers, such as polyvinyl methyl ether; polyvinylidene halides, such as polyvinylidene fluoride and polyvinylidende chloride; polyacrylonitrile, polyvinyl ketones; polyvinyl aromatics, such as polystyrene, polyvinyl esters, such as polyvinyl acetate; copolymers of vinyl monomers with each other and olefins, such as ethylene-methyl methacrylate copolymers, actrylonitrilestyrene copolymers, ABS resins, and ethylene-vinyl acetate copolymers; polyamides, such as Nylon 66 and polycaprolactam; alkyl resins; polycarbonates: polyoxymthylenes; polyimides; polyethers; epoxy resins, polyurethanes; rayon; rayon-triacetate; cellulose, cellulose acetate, cellulose butyrate; cellulose acetate butyrate; cellophane; cellulose nitrate; cellulose propionate; cellulose ethers, carboxymethyl cellulose and hydrophylic polymetacrylates. The ratio of therapeutic substance to polymer in the solution will depend on the efficacy of the polymer in securing the therapeutic substance into the perforated prothesis and the rate at which the coating is to release the therapeutic substance to the tissue of the blood vessel or body conduit. More polymer may be needed if it has relatively poor efficacy in retaining the therapeutic substance in the perforated prothesis and more polymer may be needed in order to provide an elution matrix that limits the elution of a very soluble therapeutic substance. A wide ratio of therapeutic substance to polymer could therefore be appropriate and the weight ratio could range from about 10:1 to 1:100. The therapeutic substance used in the present invention could be virtually any therapeutic substance which possesses desirable therapeutic characteristics for application to a blood vessel or body conduit. This can include both solid substances and liquid substances. For example, glucocorticoids (e.g. methyl prednisolone, dexamethasone, betamethasone), heparin, hirudin, tocopherol, angiopeptin, aspirin, ACE inhibitors, A2 blockers, beta blockers, growth factors, oligonucleotides, and, more generally, antiplatelet agents, anticoagulant agents, antimitotic agents, antioxidants, antimetabolite agents, and anti-inflammatory agents could be used. Antiplatelet agents can include drugs such as aspirin and dipyridamole. Anticoagulant agents can include drugs such as heparin, coumadin, protamine, hirudin and tick anticoagulant protein. Antimitotic agents and antimetabolite agents can include drugs such as methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, adriamycin and mitomycin. Furthermore this perforated perforated prothesis can be used to deliver genes that code for substances that can influence the foreign body reaction to the prothesis or modify the healing response induced by tissue damage.

DESCRIPTION OF THE PERFORATED PROTHESIS IN ORDER TO OBTAIN AN IMPROVED LOCAL DRUG DELIVERY DEVICE

[0091] To illustrate the invention a tubular laser cutted balloon expandable stent was used (Figure 6). Perforations of 50 µm were made using an eximer laser at a frequency of 100 Hz, pulse duration of 0.15 ms and a voltage of 510 volts. All other methods to create these holes or perforations are also suitable to obtain this invention. After conventional electrochemical polishing these stents were dipped in a polymer solution in which the drug was dissolved. For our example we used a fluorinated polymethacrylate (PFM-P75) in which 10% methyl prednisolone was dissolved. Total loading dose of methyl prednisolone loaded on a PFM-P75-coated non perforated stents was 10µg. Total loading dose of a perforated stent was 3500 µg.

[0092] In vitro release curves of the methyl prednisolone loaded PFM-P75-coated stents showed a gradually release of the methyl prednisolone over 3 weeks compared to 48 hours for the non perforated stents. Implantation of the methyl prednisolone loaded perforated stents in porcine coronary arteries using the same study protocol as for the TiN-coated stents demonstrated perfect biocompatibility of these stents. No inflammation surrounding the stent filaments was found at day 3, day 7 and day 14. At six weeks only a minimal neointimal hyperplasia was found. This invention can be used with all kind of drug or gene containing polymers and also for direct coating of drugs or genes onto the prothesis without the use of a polymer.

AIM

[0093] This invention has the following objectives:

1. to deliver a radially expandable prothesis with minimal axial shortening at radial expansion,
2. another objective is to deliver a prothesis that is sufficiently flexible so that the central axis also bends, mainly when the prothesis is introduced via the patient's arteries,
3. to deliver an intraluminal prothesis with little or none axial shortening,
4. to deliver an intraluminal prothesis of which the extremities consist of radiopaque material that is easily visible using a medical monitoring system,
5. to deliver an intraluminal prothesis consisting of a series of filaments forming peripheral elements describing a cylindrical contour, the individual filaments are put together by means of connecting parts acting as axial filaments restraining the filaments to shorten during the expansion,
6. to deliver an intraluminal prothesis having the necessary force to strengthen a lumen at implantation and at expansion,
7. to deliver an intraluminal prothesis that can be placed in a lumen by a physician respecting a high level of location precision,
8. to deliver a more biocompatible intraluminal prothesis, by using water guided laser technology,
9. to deliver a more biocompatible intraluminal prothesis, by using specific electrochemical polishing techniques,
10. to deliver a more biocompatible intraluminal metal prothesis, by covering the prothesis with a titaniumnitride coating,
11. to deliver an intraluminal locally medicine administering system.

[0094] Other objectives of the invention will become obvious by reading attentively the enclosed description and claims, and by viewing the pictures.

Claims

1. A radial expandable prothesis for implantation in a lumen, for example an artery, having a general cylindrical contour before as well as after expansion. The above-mentioned prothesis is cut from a metal cylinder using water guided laser technology, limiting in this way the heat penetration. By using water guided laser technology there is less deformation of the metal grain structure and less oxidation and corrosion of the metal surface. By utilizing the water guided laser technology, a more biocompatible prothesis is obtained causing less thrombogenicity and less foreign body reaction after implantation.

2. A radial expandable nitinol prothesis for implantation in a lumen, for example an artery, having a general cylindrical contour before as well as after expansion. The above-mentioned nitinol prothesis is pre-treated with a solution containing hydrofluoric acid and nitric acid, more optimal 1 to 5 ml of hydrofluoric acid and 10 to 100 ml of nitric acid 6 to 20M, more optimal 2 ml of hydrofluoric acid and 40 ml of nitric acid (14M) for 2 to 20 minutes, more optimal 5 to 7 minutes. After the pre-treatment, electrochemical polishing is performed using a solution of perchloric acid and acetic acid, more optimal 1 to 10 ml of perchloric acid, and 20 to 500 ml of acetic acid (99.8%), more optimal 5 ml of perchloric acid (70%) and 100 ml of acetic acid (99.8%), using an anodic current of 0.05 to 0.5 amp, more optimal 0.15 amp and a voltage of 1 to 50 V, more optimal 20 V during 0.5 to 10 minutes, more optimal 1 to 3 minutes, more optimal 1.5 to 2 minutes, resulting in a smooth surface, a decreased thrombogenicity and a decreased foreign body reaction after deployment in a life stream conduit.

3. A radial expandable tantalum prothesis for implantation in a lumen, for example an artery, having a general cylindrical contour before as well as after expansion. The above-mentioned tantalum prothesis is pre-treated with a solution containing hydrofluoride, hydrosulphate, hydronitrate and water, more optimal 1 to 10 ml of hydrofluoride (20-80%), 0.5 to 5 ml of hydrosulphate (80-99%), 2 to 20 ml of hydronitrate and 4 to 12 ml of water, more optimal 5.6 ml of of hydrofluoride (48-51%), 1 ml of hydrosulphate (95-97%), 8 ml of hydronitrate and 8 ml of water. Electrochemical polishing is performed using a solution of either acetic acid, hydrosulphate and hydrofluoride or a solution of hydrosulphate and hydrofluoride, more optimal 10 to 30 ml of acetic acid, 20 to 80 ml of hydrosulphate and 5 to 20 ml of hydrofluoride, or a solution of 70 to 120 ml of hydrosulphate and 5 to 20 ml of hydrofluoride, more optimal a solution of either 20 ml of acetic acid, 50 ml of hydrosulphate and 10 ml of hydrofluoride or a solution of 90 ml of hydrosulphate and 10 ml of hydrofluoride, using a voltage of 3 to 10 V, more optimal 5 V during a period of 1 to 5 minutes, more optimal 2 minutes.

4. A radial expandable prothesis for implantation in a lumen, for example an artery, having a general cylindrical contour before as well as after expansion. The above-mentioned prothesis is covered with a homogeneous coating of titaniumnitride of at least 0.2 μm and maximum 0.5 mm, and more optimal 1 to 10 μm. By covering the prothesis with titaniumnitride a more biocompatible intraluminal prothesis is obtained causing less thrombogenicity and less foreign body reaction after implantation.

5. A radial expandable prothesis for implantation in a lumen, for example an artery, having a general cylindrical contour before as well as after expansion. In the above-mentioned prothesis little perforations of 0.001 to 50 μm, more optimal 2 to 20 μm are made using water guided laser technology or any other technology. Next these perforations or holes are filled up with a medicine or a with medicine impregnated polymer. By using the perforated prothesis, the capacity to locally administer medicines or other substances is significantly increased. Furthermore the local drug release is significantly prolonged. This local drug delivery system results in an increased patency of the implanted endoluminal prothesis.

6. A radial expandable prothesis for implantation in a lumen, for example an artery, having a general cylindrical contour before as well as after expansion. In the above-mentioned prothesis little perforations of 0.001 to 50 μm, more optimal 2 to 20 μm are made using water guided laser technology or any other technology. Next these perforations or holes are filled up with a gene or a with gene impregnated polymer. By using the perforated prothesis the capacity to locally administer genes or other substances is increased significantly.

7. A radial expandable prothesis for implantation in a lumen, for example an artery, having a general cylindrical contour before as well as after expansion. In the above-mentioned prothesis holes of 0.001 to 50 μm width and 0.001 μm to 0.1 mm depth, more optimal 2 to 20 μm width and 0.1 to 0.5 mm depth, are applied using water guided laser technology or any other technology. By this handling the capacity to locally administer medicines or other substances is increased significantly. The above-mentioned prothesis with holes is covered with a medicine and or a gene or a with medicine or gene impregnated polymer. The result is a prothesis gradually releasing medicines and or genes locally. By using the prothesis with holes, the total medicine capacity is increased significantly and also the medicine or gene release time is prolonged significantly. This local drug or gene delivery system results in an increased patency of the implanted endoluminal prothesis.

8. By pointing the holes along the inner or the outer side of any radial expandable prothesis for implantation in a lumen, for example an artery, the locally releasing of medicines, genes or other substances can be directed either towards the lumen, or towards the tissue surrounding the lumen.

Figure 1. Typical configuration of the omega radial expandable prothesis

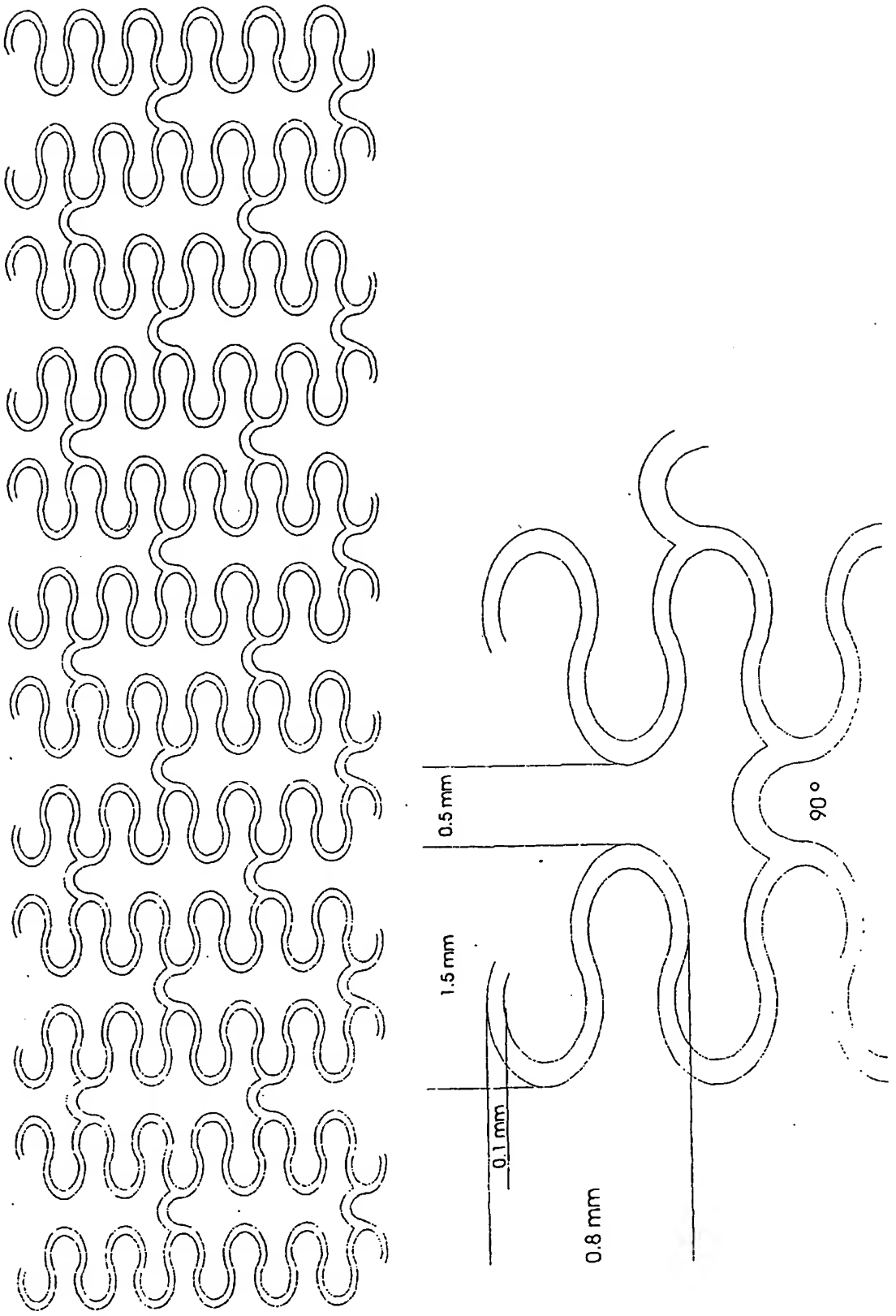
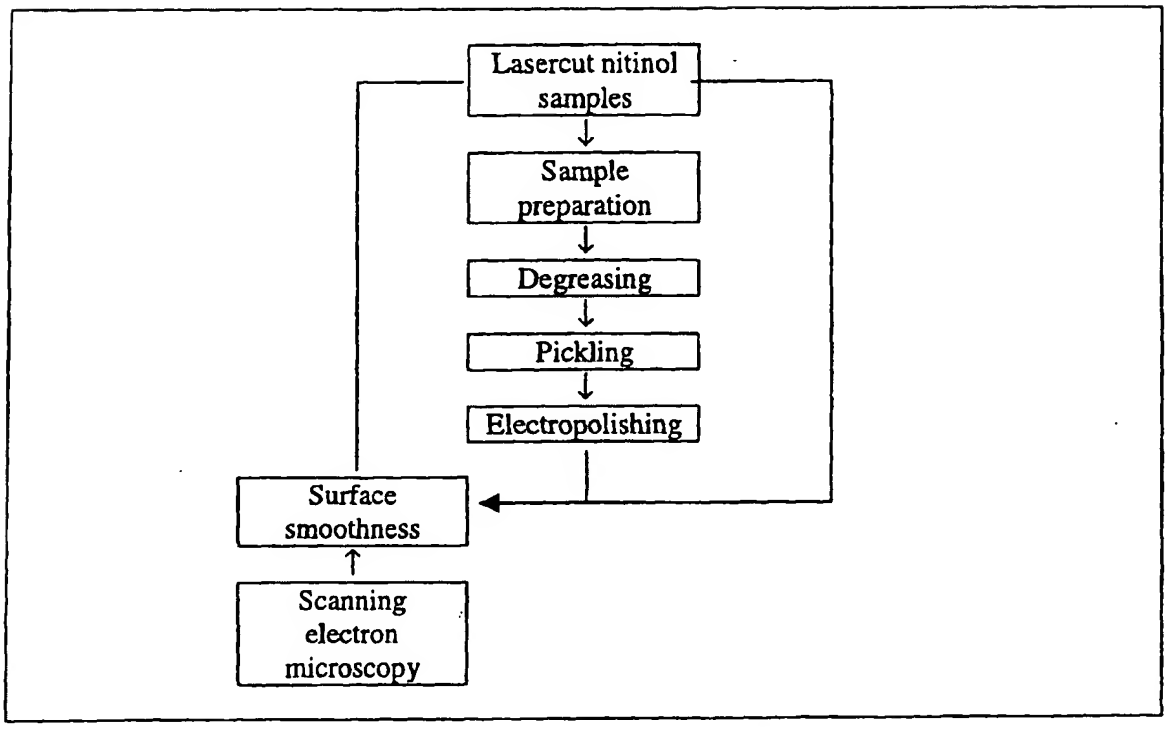


Figure 2. Electochemical polishing of nitinol samples



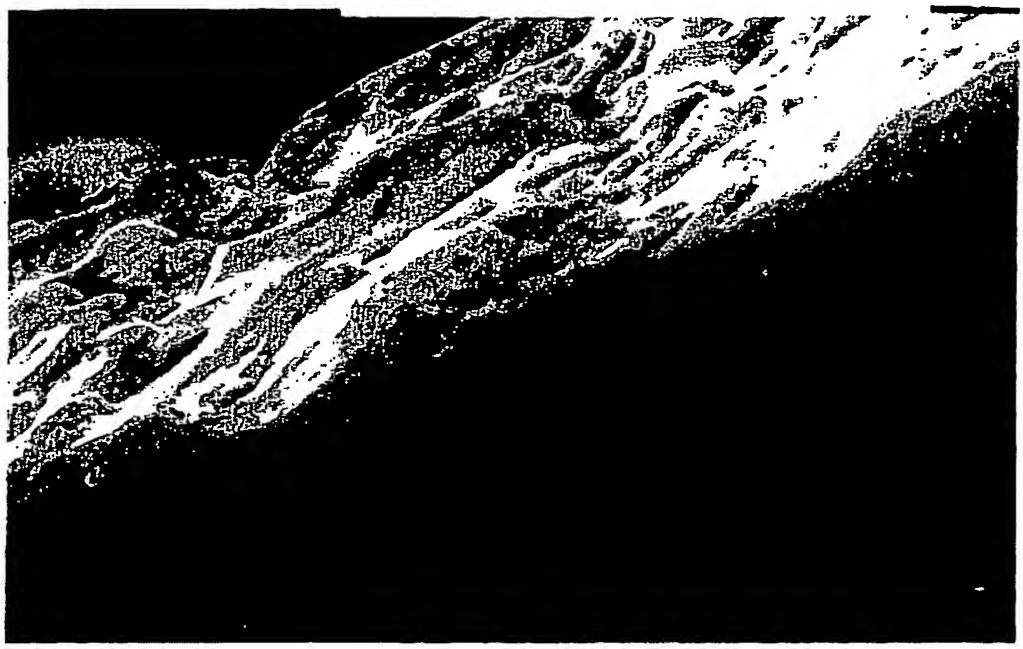


Figure 3 (a). Roughness of the as-received nitinol alloy stent (the side surface) (680x)

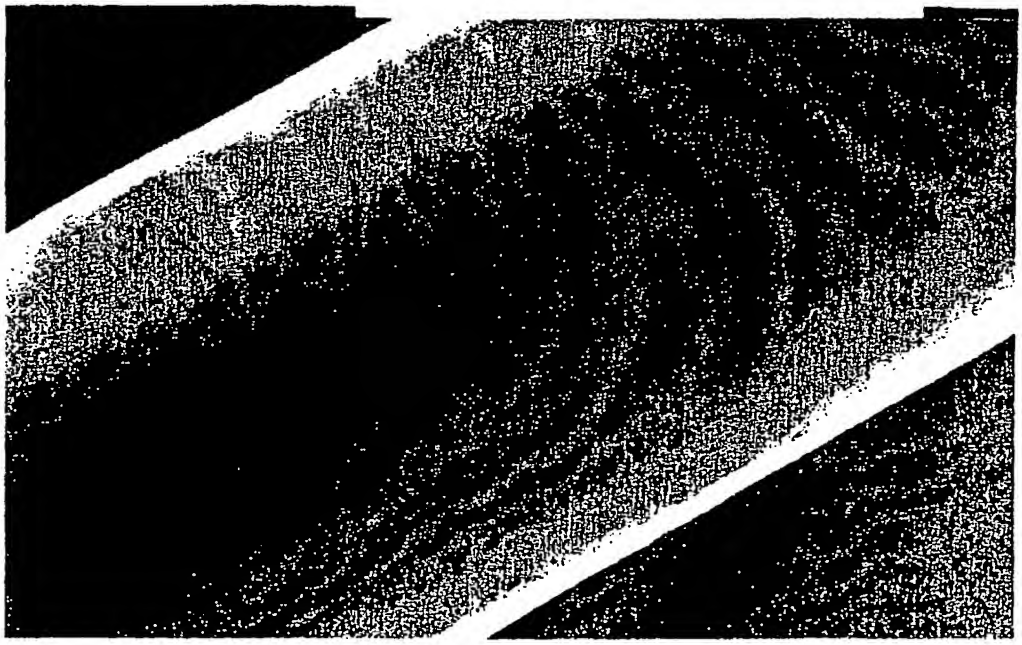


Figure 3 (b). The electrochemically polished nitinol alloy stent (655x)

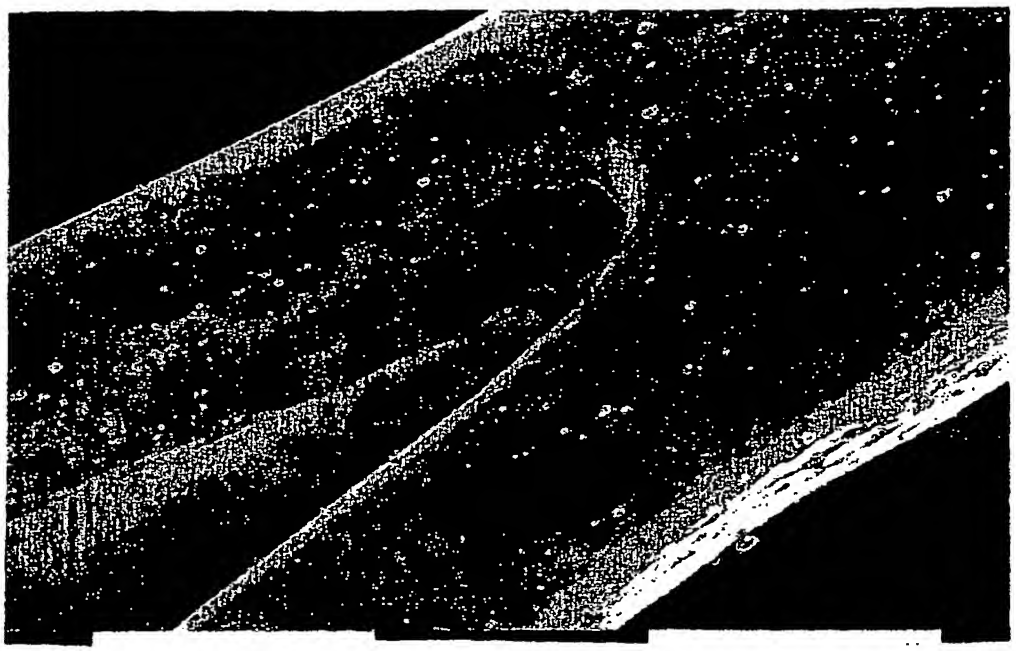


Figure 4 (a). The overpolished surface of a nitinol alloy stent (326x)

Figure 4 (b). The overpolished surface of a nitinol alloy stent (326x)

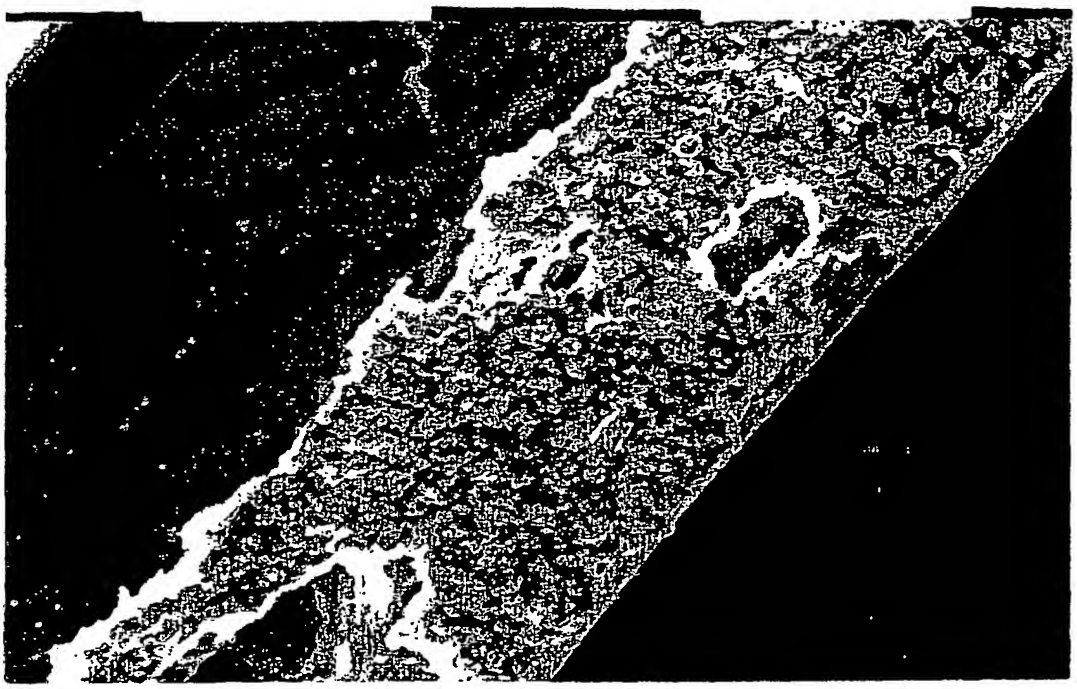
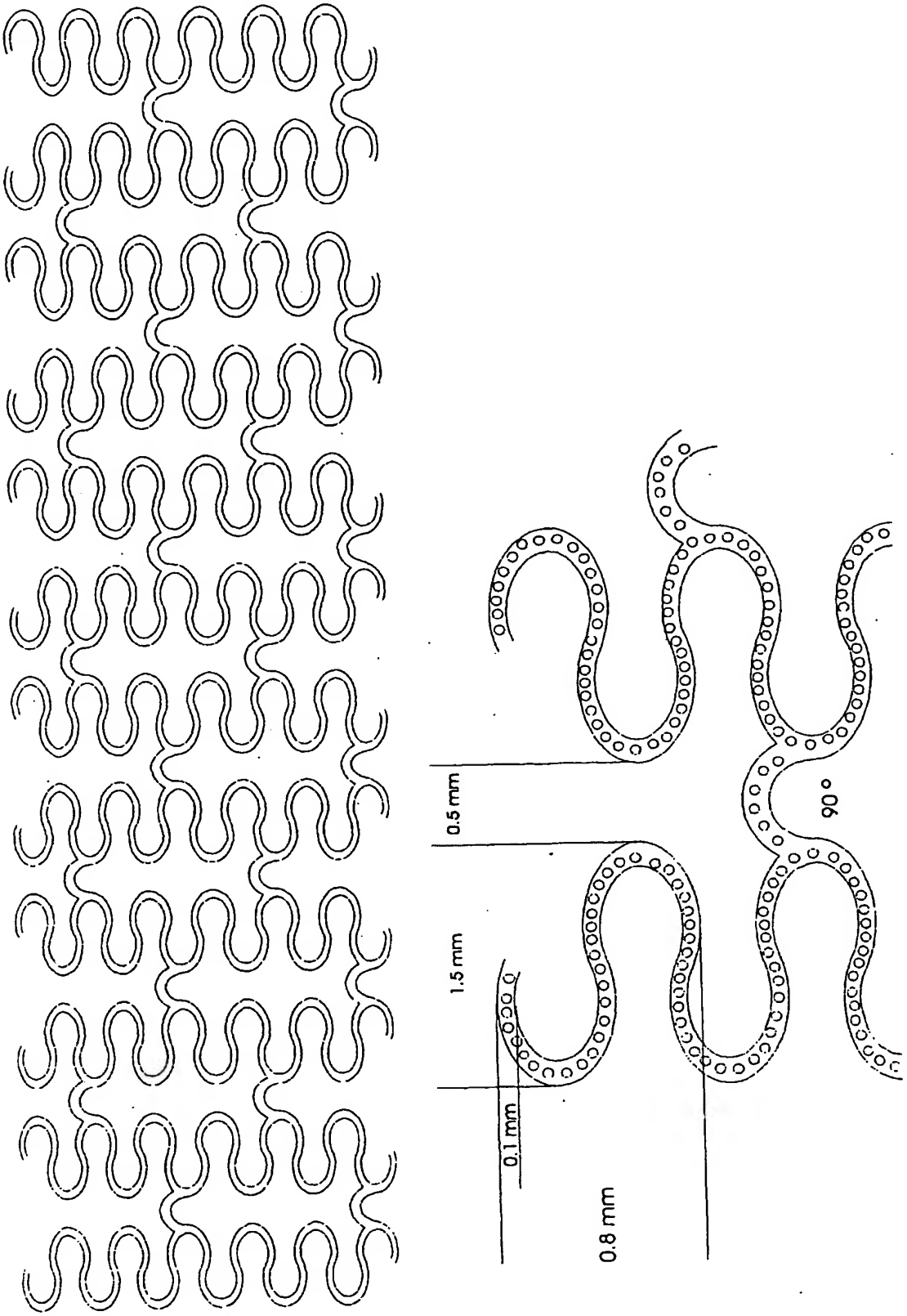


Figure 5. The bottom surface of an electrochemical polished nitinol alloy stent without pickling (300x)

Figure 6. Typical configuration of the perforated omega radial expandable prothesis



European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 87 0035

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	DE 199 16 086 A (INFLOW DYNAMICS INC.) 14 October 1999 (1999-10-14) * column 3, line 9 - line 38; figures *	4	A61F2/06
A	EP 0 931 520 A (ADVANCED CARDIOVASCULAR SYSTEMS, INC.) 28 July 1999 (1999-07-28) * column 11, line 41 - column 15, line 29 *	1-3	
A	WO 98 51238 A (NOVO RPS ULC) 19 November 1998 (1998-11-19) * page 17, line 20 - page 18, line 11 *	2,3	
X	WO 99 16386 A (SCIMED LIFE SYSTEMS, INC.) 8 April 1999 (1999-04-08)	5,8	
Y	* the whole document *	6,7	
Y	EP 0 950 386 A (CORDIS CORPORATION) 20 October 1999 (1999-10-20) * the whole document *	6,7	
X	WO 98 23228 A (ALZA CORPORATION) 4 June 1998 (1998-06-04) * the whole document *	5,8	TECHNICAL FIELDS SEARCHED (Int.Cl.7) A61F
A	US 5 902 266 A (LEONE ET AL) 11 May 1999 (1999-05-11) * the whole document *	5-8	

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	16 November 2000	Smith, C

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C01)

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Application Number
EP 00 87 0035

CLAIMS INCURRING FEES

The present European patent application comprised at the time of filing more than ten claims.

☐ Only part of the claims have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims and for those claims for which claims fees have been paid, namely claim(s):

☐ No claims fees have been paid within the prescribed time limit. The present European search report has been drawn up for the first ten claims.

LACK OF UNITY OF INVENTION

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

see sheet B

☒ All further search fees have been paid within the fixed time limit. The present European search report has been drawn up for all claims.

☐ As all searchable claims could be searched without effort justifying an additional fee, the Search Division did not invite payment of any additional fee.

☐ Only part of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the inventions in respect of which search fees have been paid, namely claims:

☐ None of the further search fees have been paid within the fixed time limit. The present European search report has been drawn up for those parts of the European patent application which relate to the invention first mentioned in the claims, namely claims:

European Patent Office

LACK OF UNITY OF INVENTION
SHEET B

Application Number
EP 00 87 0035

The Search Division considers that the present European patent application does not comply with the requirements of unity of invention and relates to several inventions or groups of inventions, namely:

1. Claims: 1-4

   Surface treatment of stent

2. Claims: 5-8

   Stent with perforations loaded with therapeutic agent

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 87 0035

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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